

**Preliminary Amendment**

National Stage Entry of PCT/JP03/02981

Attorney Docket No.: Q87415

**AMENDMENTS TO THE CLAIMS**

**This listing of claims will replace all prior versions and listings of claims in the application:**

**LISTING OF CLAIMS:**

1.-16. (canceled).

17. (original): A method for accelerating production of an endogenous repair factor in a mammal, which comprises administering to a mammal an effective amount of one or at least two selected from a PGI2 agonist, an EP2 agonist and an EP4 agonist.

18. (original): A method for preventing and/or treating organ diseases in a mammal, which comprises administering to a mammal an effective amount of one or at least two selected from a PGI2 agonist, an EP2 agonist and an EP4 agonist.

19. (canceled).

20. (canceled).

21. (currently amended): A pharmaceutical composition which comprises the endogenous repair factor production accelerator ~~according to claim 1~~ comprising one or least two selected from a PG12 agonist, an EP2 agonist and an EP4 agonist in combination with one or at least two selected from an anti-thrombus agent, a circulation improving agent, a bronchial smooth muscle dilator, an anti-inflammatory drug, a local anesthetic, an analgesic, a bone cement, an joint lubricant, a PG derivative, an endogenous repair factor protein, an endogenous repair factor gene and a stem cell.

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22. (New): The method according to claim 17, wherein the endogenous repair factor is a vascular endothelial growth factor, a hepatocyte growth factor, a fibroblast growth factor, a transformation growth factor- $\beta$ , a platelet derived growth factor, a bone morphogenetic protein or an epidermal growth factor.

23. (New): The method according to claim 17, wherein stem cell differentiation is induced.

24. (New): The method according to claim 17, wherein angiogenesis is accelerated.

25. (New): The method according to claim 17, wherein the PGI2 agonist, the EP2 agonist or the EP4 agonist is administered as a persistent preparation which further comprises a biodegradable polymer.

26. (New): The method according to claim 25, wherein the persistent preparation is a microsphere preparation, a microcapsule preparation or a nanosphere preparation.

27. (New): The method according to claim 17, wherein organ diseases are prevented and/or treated.

28. (New): The method according to claim 27, wherein the organ disease is an ischemic organ disease, a liver disease, a kidney disease, a lung disease, a pancreas disease, a bone disease, a digestive organ disease, a nerve degeneration disease, a diabetic complication, a vascular endothelial cell disease, a heart disease, a dental disease, decubitus, glaucoma or alopecia.

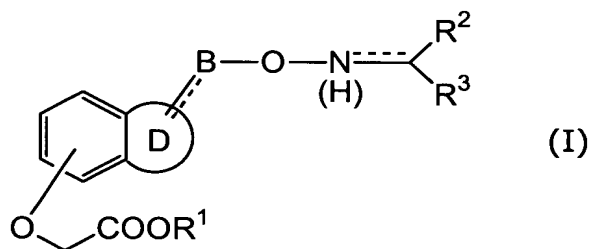
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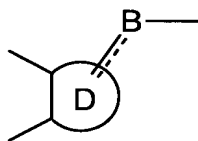
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29. (New): The method according to claim 28, wherein the ischemic organ disease is arteriosclerosis obliterans, Buerger disease, Raynaud disease, myocardial infarction, angina pectoris, diabetic neuropathy, spinal canal stenosis, cerebrovascular accidents, cerebral infarction, pulmonary hypertension, bone fracture or Alzheimer disease.

30. (New): The method according to claim 17, wherein the PGI<sub>2</sub> agonist is a compound represented by formula (I):



wherein

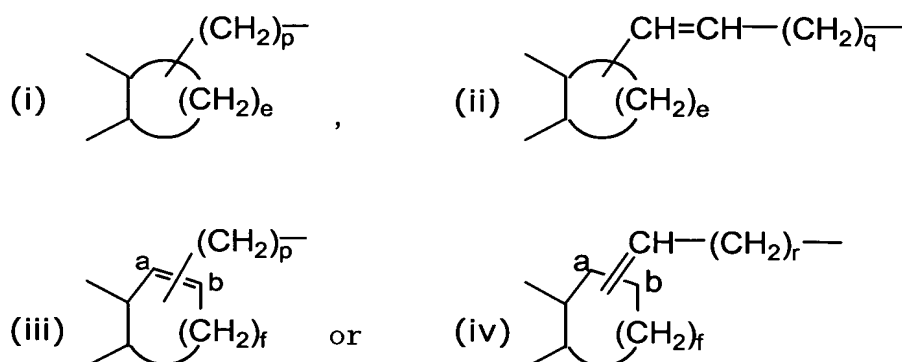


is

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wherein  $R^1$  represents hydrogen or C1-4 alkyl;

$R^2$  represents (i) hydrogen, (ii) C1-8 alkyl, (iii) phenyl or C4-7 cycloalkyl, (iv) a 4- to 7-membered monocyclic ring containing one nitrogen atom, (v) C1-4 alkyl substituted with a benzene ring or C4-7 cycloalkyl, or (vi) C1-4 alkyl substituted with a 4- to 7-membered monocyclic ring containing one nitrogen atom;

$R^3$  represents (i) C1-8 alkyl, (ii) phenyl or C4-7 cycloalkyl, (iii) a 4- to 7-membered monocyclic ring containing one nitrogen atom, (iv) C1-4 alkyl substituted with a benzene ring or C4-7 cycloalkyl, or (v) C1-4 alkyl substituted with a 4- to 7-membered monocyclic ring containing one nitrogen atom;

e represents an integer of from 3 to 5;

f represents an integer of from 1 to 3;

p represents an integer of from 1 to 4;

r represents an integer of from 1 to 3;

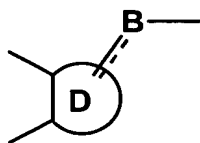
q represents an integer of 1 or 2, and

wherein, when

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is the group represented by (iii) or (iv),

$-(CH_2)_p-$  and  $=CH-(CH_2)_s-$  are bound to the position of a or b on the ring, and

the rings in  $R^2$  and  $R^3$  may be substituted with 1 to 3 of C1-4 alkyl, C1-4 alkoxy, halogen, nitro or trihalomethyl, or

a salt thereof.

31. (New) The method according to claim 30, wherein the PGI2 agonist is

- (1) (E)-[5-[2-[1-phenyl-1-(3-pyridyl)methylideneaminoxy]ethyl]-7,8-dihydronaphthalen-1-yloxy]acetic acid, or
- (2) (Z)-[5-[2-[1-phenyl-1-(3-pyridyl)methylideneaminoxy]ethyl]-7,8-dihydronaphthalen-1-yloxy]acetic acid.

32. (New): The method according to claim 17, wherein the PGI2 agonist is

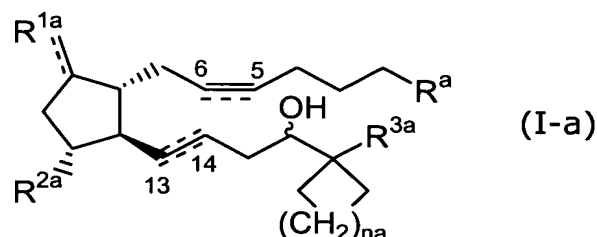
- (1)  $(\pm)$ -(1R,2R,3aS,8bS)-2,3,3a,8b-terahydro-2-hydroxy-1-[(E)-(3S,4RS)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1H-cyclopenta[b]benzofuran-5-butanoic acid sodium salt,
- (2) 5-[(3aR,4R,6aS)-5-hydroxy-4-[(1E,3S)-3-hydroxy-3-(cis-4-propylcyclohexyl)prop-1-enyl]-3,3a,4,5,6,6a-hexahydrocyclopenta[b]pyrrol-2-yl]pentanoic acid methyl ester, or
- (3) (5E)-5-[(3aS,4R,5R,6aS)-4-[(1E,3S)-3-cyclopentyl-3-hydroxyprop-1-enyl]-5-hydroxyhexahydropentalene-2(1H)-ylidene]pentanoic acid.

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33. (New): The method according to claim 17, wherein the EP2 agonist is a compound represented by formula (I-a):



wherein  $R^a$  represents carboxyl or hydroxymethyl;

$R^{1a}$  represents oxo, methylene or halogen;

$R^{2a}$  represents hydrogen, hydroxyl or C1-4 alkoxy;

$R^{3a}$  represents hydrogen, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, or C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted with 1 to 3 of the following groups (1) to (5): (1) halogen, (2) C1-4 alkoxy, (3) C3-7 cycloalkyl, (4) phenyl, (5) phenyl substituted with 1 to 3 halogen, C1-4 alkyl, C1-4 alkoxy, nitro or trifluoromethyl;

$na$  represents 0 or an integer of from 1 to 4;

$\equiv$  represents a single bond or a double bond;

$\equiv$  represents a double bond or a triple bond; and

$\equiv$  represents a single bond, a double bond or a triple bond, and

wherein (1) when the 5-6 position represents a triple bond, the 13-14 position does not represent a triple bond, and

(2) when the 13-14 position represents a double bond, the a double bond represents E form, Z form or EZ form,

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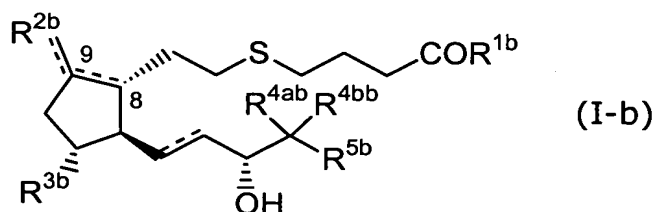
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a salt thereof, a prodrug thereof or a cyclodextrin clathrate thereof.

34. (New): The method according to claim 33, wherein the EP2 agonist is (5Z,9 $\beta$ ,11 $\alpha$ ,13E)-17,17-propano-11,16-dihydroxy-9-chloro-20-norprost-5,13-dienoic acid.

35. (New): The method according to claim 17, wherein the EP4 agonist is a compound represented by formula (I-b):



wherein R<sup>1b</sup> represents hydroxyl, C1-6 alkoxy or -NR<sup>6b</sup>R<sup>7b</sup>;

R<sup>6b</sup> and R<sup>7b</sup> each independently represents hydrogen or C1-4 alkyl;

R<sup>2b</sup> represents oxo, halogen or -O-COR<sup>8b</sup>;

R<sup>8b</sup> represents C1-4 alkyl, phenyl or phenyl(C1-4 alkyl);

R<sup>3b</sup> represents hydrogen or hydroxyl;

R<sup>4ab</sup> and R<sup>4bb</sup> each independently represents hydrogen or C1-4 alkyl;

R<sup>5b</sup> represents phenyl substituted with a group of the following i) to iv):

i) 1 to 3 of

C1-4 alkoxy-C1-4 alkyl,

C2-4 alkenyloxy-C1-4 alkyl,

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C2-4 alkynyloxy-C1-4 alkyl,  
C3-7 cycloalkyloxy-C1-4 alkyl,  
C3-7 cycloalkyl(C1-4 alkoxy)-C1-4 alkyl,  
phenyloxy-C1-4 alkyl,  
phenyl-C1-4 alkoxy-C1-4 alkyl,  
C1-4 alkylthio-C1-4 alkyl,  
C2-4 alkenylthio-C1-4 alkyl,  
C2-4 alkynylthio-C1-4 alkyl,  
C3-7 cycloalkylthio-C1-4 alkyl,  
C3-7 cycloalkyl(C1-4 alkylthio)-C1-4 alkyl,  
phenylthio-C1-4 alkyl, or  
phenyl-C1-4 alkylthio-C1-4 alkyl,  
ii) C1-4 alkoxy-C1-4 alkyl and C1-4 alkyl,  
C1-4 alkoxy-C1-4 alkyl and C1-4 alkoxy,  
C1-4 alkoxy-C1-4 alkyl and hydroxy,  
C1-4 alkoxy-C1-4 alkyl and halogen,  
C1-4 alkylthio-C1-4 alkyl and C1-4 alkyl,  
C1-4 alkylthio-C1-4 alkyl and C1-4 alkoxy,  
C1-4 alkylthio-C1-4 alkyl and hydroxy, or



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C1-4 alkylthio-C1-4 alkyl and halogen,

iii) haloalkyl or hydroxy-C1-4 alkyl, or

iv) C1-4 alkyl and hydroxy; and

----- represents a single bond or a double bond, and

wherein, when R<sup>2b</sup> is -O-COR<sup>8b</sup>, the 8-9 position represents a double bond,

a salt thereof or a cyclodextrin clathrate thereof.

36. (New): The method according to claim 35, wherein the EP4 agonist is

(1) (11 $\alpha$ ,13E,15 $\alpha$ )-9-oxo-11,15-dihydroxy-16-(3-methoxymethylphenyl)-17,18,19,20-tetranor-5-thiaprost-13-enoic acid, or

(2) (11 $\alpha$ ,13E,15 $\alpha$ )-9-oxo-11,15-dihydroxy-16-(3-methoxymethylphenyl)-17,18,19,20-tetranor-5-thiaprost-13-enoic acid methyl ester.